Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 61, 63-90 and 92-126 are pending in the application, with claims 61 and 90 being the independent claims. Claims 61 and 90 are sought to be amended by the present amendment. Claims 1-60, 62, and 91 were previously canceled without prejudice to or disclaimer of the subject matter therein.

Claims 61 and 90 have been amended to more clearly define Applicants' invention. Support for the amendments to claims 61 and 90 can be found in the specification, e.g., at page 4, lines 4-13 and 33-36; at page 5, lines 1-11; at page 6, lines 1-1; and at page 23, lines 10-15.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Request for Interview with Examiner

Applicants respectfully request the Examiner to grant an in-person interview prior to issuing a further Office Action. Applicants believe that it would advance prosecution if the undersigned could explain the significance of various claim limitations and how the claims distinguish over the prior art.

II. The Claimed Invention

Applicants' invention as presently claimed is directed to comparative high throughput, parallel screening methods for comparing the pharmacological effects of test substances. The claimed methods are based on cellular assays and measure and then compare the effects of the test substances on the activities of biological target molecules in test cells. The claimed methods comprise (a) selecting from a cell population test cells of the same type but containing different biological target molecules (or of different types but containing the same biological target molecule); (b) applying under the control of a robot test substances in parallel to sets of the test cells selected in (a), wherein a defined amount of a test substance from the same supply is applied simultaneously to a set of the test cells, the set comprising test cells selected in (a) of the same type but containing different biological target molecules (or of different types but containing the same biological target molecule); (c) measuring the effects of the test substances applied in (b) on the biological activities of the different biological target molecules (or on the activity of the same biological target molecule) in the test cells using a detection system, wherein (i) the detection system is coupled to activation of the different biological target molecules (or of the biological target molecule in cells containing the same biological target molecule) or (ii) the detection system is coupled to one or more regulatory mechanisms triggered by activation of the different biological target molecules (or of the biological target molecule in cells containing the same biological target molecule); and (d) directly or indirectly comparing with one another the effects of the test substances on the activities of the different biological target molecules (or on the activity of the biological target molecule) measured in (c).

In some embodiments (e.g., in the method of claim 61), the test cells contain different biological target molecules but are of the same type (see, e.g., the specification, at page 10, lines 9-17, and Example 1, at pages 25 to 43). In other embodiments (e.g., in the method of claim 90), the test cells contain the same biological target molecules but are of different types or of the same type but with a different state of differentiation or activation (see, e.g., the specification, at page 10, lines 19-31). A discussion of different biological target molecules appears in the specification, e.g., at page 9, lines 15-29; a discussion of cell types appears at page 8, lines 4-25.

A central feature of the claimed methods is that each test substance is applied simultaneously (*i.e.*, at the same time), under the control of a robot, to a set of test cells using the same source of test substance (see, e.g., the specification, at page 4, lines 10-13). In the method of claim 61, the set of test cells comprises a group of test cells of the same type but containing different target molecules. In the method of claim 90, the set of test cells comprises either (i) a group of test cells of different types which contain the same target molecule, or (ii) a group of test cells of the same type but with a different state of differentiation or activation, which contain the same biological target molecule.

Simultaneous application of each test substance to a set of different test cells (*i.e.*, application of the test substance to the different cells *at the same time*), using test substance from the *same source*, minimizes the variables associated with use of the different assays or assay formats that are required to measure the effect of the test substance in the different test cells. This allows for a better comparison and evaluation of the effect of the substance in the different test cells. See the specification, e.g., at page 4, lines 10-13, and page 6, lines 1-9.

Multiple test substances are then screened by parallel application to sets of test cells ("parallel screening"), allowing for high throughput screening of the test substances. For example, the specification, at page 6, lines11-17, states that parallel screening is generally screening "whereby a number of different assays or assay formats are carried out with the same arrangement of equipment under the control of a robot."

III. Rejections under 35 U.S.C. § 102

Claims 61, 67-69, 76, 81-85, 87-90, 105, 110-114, and 116-126 are rejected under 35 U.S.C. § 102(b) for allegedly being anticipated by Harpold *et al.*, International Publ. No. WO 92/02639 ("Harpold"). (Office Action, at page 3, lines 1-2.) Applicants respectfully traverse this rejection.

Specifically, the Examiner states that "Harpold *et al.* teach high throughput parallel screening method (multiple well-format) of claims 61, 90 . . . ." (Office Action, at page 3, lines 3-4.) In particular, the Examiner alleges that Harpold teaches the limitations of step (b) of claims 61 and 90, stating:

> (b) applying from the same supply a defined amount (1.4 nM) of test substances (antagonists and agonists) to one or more set of test cells of the same type comprising more than one cellular substrates (receptors), which differ in that they contain different target molecules (different receptors) (see page 38, line 25-36, page 39, line 1-36, example 3, page 41, line 4-27);

(Office Action, at page 3, lines 12-15.) The Examiner goes on to allege that the specific limitations of the listed dependent claims are also taught, concluding that "[a]ccordingly, Harpold *et al.* anticipates the instant claims." (Office Action, at page 4, line 15.)

For rejections under 35 U.S.C. § 102, the Federal Circuit held "[a] claim is anticipated only if *each and every element* as set forth in the claim is found, either

expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 613, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (emphasis added).

Applicants respectfully assert that Harpold fails to teach each and every element of the comparative high throughput parallel screening method of pending independent claims 61 and 90, and their dependent claims 67-69, 76, 81-85, 87-89, 105, 110-114, and 116-126, each of which incorporates the elements of claims 61 and 90.

In particular, Harpold fails to teach step (b) and/or step (c) of claims 61 and 90. Step (b) of these claims recites applying under the control of a robot test substances in parallel to sets of test cells, wherein a defined amount of a test substance from the same supply is applied simultaneously to a set of said test cells, the set comprising test cells of the same type but containing different biological target molecules (claim 61), or comprising test cells of different types but containing the same biological target molecule (claim 90). Step (c) recites measuring the effects of the test substances on the biological activities of the different biological target molecules (claim 61) or on the activity of the same biological target molecule (claim 90) in the test cells using a detection system that is either (i) coupled to activation of the different biological target molecules (claim 61) or of the biological target molecule in cells containing the same biological target molecule (claim 90) or (ii) coupled to one or more regulatory mechanisms triggered by activation of the different biological target molecules (claim 61) or of the biological target molecule in cells containing the same biological target molecule (claim 90).

In the passages cited by the Examiner (Example 3, at page 38, lines 25-36, page 39, lines 1-36, and page 41, lines 4-27), Harpold appears to disclose the results of two sets of experiments: (1) competitive binding experiments measuring the ability of the disclosed transcription-based assay to detect agonists and antagonists of the human M1 ("HM1") muscarinic receptor (page 39, lines 22-36, to page 40, lines 1-25); and (2) phosphatidyl inositol ("PI") hydrolysis experiments measuring the ability of the assay system to detect the pharmacological effect of a compound on the HM1 receptor: activation of the HM1 receptor by an agonist resulting in activation of the PI hydrolysis cascade, a signal transduction pathway (page 40, lines 26-36, to page 43, line 29).

The experiments in Harpold employ a number of recombinant cell lines containing a plasmid with DNA encoding the HM1 receptor and/or a c-fos-CAT reporter plasmid. Both experiments employ four recombinant cell lines (LM159-10, LM124-3, LM1FC4-8, and LM1FC4-15) each of which express the HM1 receptor on the cell surface, and 3 control cell lines (SH-SY5Y, PC12, and 59-0). All four recombinant cell lines are derived from Ltk+ cells and are thus of the same cell type. Two of the recombinant cell lines (LM1FC4-8, and LM1FC4-15), in addition, contain the c-fos-CAT reporter construct. The other two recombinant cell lines (LM159-10, LM124-3) do not contain the reporter construct. All four recombinant cell lines express the same receptor, HM1, which is the one biological target molecule of the assay. Of the three control cell lines used in the experiment, the 59-0 line is of the same type as the four recombinant cell lines (derived from Tk+ cells) but does not express HM1 receptor. The other two control cell lines, SH-SY5Y and PC12, are of a difference cell type from the four recombinant cell lines, but do express HM1 receptor endogenously. See Harpold, at

page 37, line 15, to page 38, line 25; page 23, lines 8-16; page 28, lines 18-30; page 31, lines 10-19; and page 35, line 25, to page 36, line 20.

Applicants submit that both the competitive binding and PI hydrolysis experiments disclosed in Harpold fail to teach each and every element of steps (b) and/or (c) in pending claim 61. In particular, the competitive binding experiment in Harpold fails to teach step (b) of the high throughput parallel screening method of claim 61, because step (b) of claim 61 as presented requires that a test compound be applied to a set of test cells of the same type but containing different biological target molecules. In the Harpold experiments, each test cell line contains the *same* biological target molecule (HM1 receptor), not *different* biological target molecules, as recited in claim 61. Moreover, there is no indication in Harpold that the competitive binding experiment was performed according to step (b) of claim 61 as currently presented, *i.e.*, that each agonist (test substance) was applied simultaneously and from the same supply as required in claim 61, and under the control of a robot.

In addition, the competitive binding experiments fail to teach each and every element of step (c) of claim 61. Claim 61 as presented recites in step (c) that the effects of the test substances on the biological activities of the different biological target molecules are measured using a detection system that is either (i) coupled to activation of the different biological target molecules or (ii) coupled to one or more regulatory mechanisms triggered by activation of the different biological target molecules. The "detection system" used in the competitive binding experiments is the measurement of binding of a compound to the surface HM1 receptor, a process that is not coupled to

activation of the target molecule (HM1) or to a regulatory mechanism (e.g., pathway) triggered by activation of the HM1 receptor.

Similarly, the competitive binding experiments fail to teach each and every element of steps (b) and (c) in claim 90. As discussed above for claim 61, there is no indication that in the competitive binding experiments in Harpold, each agonist (test substance) was applied *simultaneously* and from the same supply as required in step (b) of claim 90, and under the control of a robot. Also, the "detection system" used in the competitive binding experiments (the measurement of binding of a compound to the surface HM1 receptor) is not a process that is coupled to activation of the target molecule (HM1) or coupled to a regulatory mechanism (e.g., pathway) triggered by activation of the HM1 receptor.

Moreover, the PI hydrolysis experiments also fail to teach each and every element of steps (b) of claims 61 and 90 as presented.

As described above for the competitive binding experiments, the PI hydrolysis experiments fail to teach all elements of step (b) of claim 61, which requires that a test compound be applied to a set of test cells of the same type but containing different biological target molecules. In the PI hydrolysis experiments, each test cell line contains the *same* biological target molecule (HM1 receptor), not different biological target molecules, as recited in claim 61. Moreover, there is no indication that in the PI hydrolysis experiment, each agonist (test substance) was applied simultaneously and from the same supply and under the control of a robot, as required in step (b) of claims 61 and 90.

Applicants thus submit that Harpold does not anticipate Applicants' pending claims because this reference fails to teach or suggest each and every element of the claims for the reasons discussed above.

Applicants believe that the rejection of 61, 67-69, 76, 81-85, 87-90, 105, 110-114, and 116-126 under 35 U.S.C. § 102(b) has been overcome and respectfully request that the rejection be withdrawn.

IV. Rejections under 35 U.S.C. § 103

In re Vaeck (947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)) outlines the factors required for establishing a *prima facie* case for obviousness: prior art references that teach all claim limitations, a motivation to combine the teachings in the references themselves or knowledge known to a person of skill in the art at the time the invention was made, and a reasonable expectation of success from the combination of elements in the references. As discussed below, Applicants respectfully assert that these requirements have not been met to support a *prima facie* argument for obviousness for the instant claims.

A. Harpold in view of Johnson

Claims 63-64, 66, 70-71, 74, 75, 77-80, 92, 93, 95, 99, 100, 103, 104, and 106-109 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Harpold in view of Johnson, International Publ. No. WO 95/28421 ("Johnson"). (Office Action, at page 5, lines 8-10.) Applicants respectfully traverse this rejection.

Specifically, the Examiner asserts that Johnson teaches a method of determining the pharmacological effect of a substance on the activity of different biological target molecules in the signal transduction pathway wherein said different target molecules comprise a receptor-coupled signal transduction pathway. (Office Action, at page 5, lines 16-19.) The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Harpold with various signaling molecules that control cell differentiation/growth/apoptosis as taught by Johnson. (Office Action, at page 6, lines 3-5.)

The deficiencies of Harpold have been discussed *supra* and remain applicable in the present rejection. Applicants submit that there would have been no reason, in light of Harpold and Johnson, for one of ordinary skill in the art at the time the invention was made to arrive at *simultaneous* application of a test substance from the same supply and under the control of a robot to a set of test cells, as recited in claims 63-64, 66, 70-71, 74, 75, 77-80, 92, 93, 95, 99, 100, 103, 104, and 106-109, or *simultaneous* application of a test substance from the same supply and under the control of a robot to a set of test cells containing *different* biological target molecules, as recited in claims 63-64, 66, 70-71, 74, 75, 77-80. Johnson merely characterizes the response of various second messenger protein kinases to various stimuli and putative regulatory compounds. *See* Johnson, at page 61, line 16 to page 62, line 23. Thus, Applicants submit that Johnson fails to overcome the deficiencies of Harpold, and the burden of a *prima facie* case for obviousness has not been met.

Accordingly, Applicants believe that the rejection of claims 63-64, 66, 70-71, 74, 75, 77-80, 92, 93, 95, 99, 100, 103, 104, and 106-109 under 35 U.S.C. § 103(a) for

allegedly being unpatentable over Harpold in view of Johnson has been overcome and respectfully request that the rejection be withdrawn.

B. Harpold in view of Johnson and further in view of Bischoff and Brown

Claims 65, 72, 73, 94, 101, and 102 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Harpold in view of Johnson as applied to claims 63, 64, 66, 70, 71, 74, 75, 77-80, 92, 93, 95, 99, 100, 103, 104, and 106-109, and further in view of Bischoff *et al.*, U.S. Pat. No. 5,705,342 ("Bischoff"), and Brown *et al.*, U.S. Pat. No. 5,929,081 ("Brown"). (Office Action, at page 6, lines 16-19.) Applicants respectfully traverse this rejection.

Specifically, the Examiner asserts that Bischoff teaches regulation of cell proliferation control and neoplasia by Bcl-2 expression and signal transduction mediated by the association between Ras and bcl-2 (Office Action, at page 7, lines 3-5), while Brown teaches a method for treating diseases mediated by cellular proliferation signal transduction pathway effector molecules, comprising treating the diseases associated with cellular target receptor molecules such as VGEF, HER2, and ras/raf pathway signalling molecules (Office Action, at page 7, lines 6-10).

The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Harpold in view of Johnson with target molecules comprising Bcl-2 as taught by Bischoff and receptors as HGF, HER2 and KDR as taught by Brown to enhance the sensitivity of the method to detect the signaling pathway as a whole. (Office Action, at page 7, lines 11-15.)

The deficiencies of Harpold and Johnson have been discussed *supra* and remain applicable in the present rejection. Applicants submit that Bischoff and Brown do not remedy the deficiencies of Harpold and Johnson, because there would have been no reason, in light of Harpold, Johnson, Bischoff and Brown, for one of ordinary skill in the art at the time the invention was made to arrive at *simultaneous* application of a test substance from the same supply and under the control of a robot to a set of test cells, as recited in claims 65, 72, 73, 94, 101, and 102, or *simultaneous* application of a test substance from the same supply and under the control of a robot to a set of test cells containing *different* biological target molecules, as recited in claims 65, 72 and 73. Thus, Applicants submit that Bischoff and Brown fail to overcome the deficiencies of Harpold and Johnson, and thus the burden of a *prima facie* case for obviousness has not been met.

Accordingly, Applicants believe that the rejection of claims 65, 72, 73, 94, 101, and 102 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Harpold in view of Johnson as applied to claims 63, 64, 66, 70, 71, 74, 75, 77-80, 92, 93, 95, 99, 100, 103, 104, and 106-109 and further in view of Bischoff and Brown has been overcome and respectfully request that the rejection be withdrawn.

C. Harpold in view of Chalfie

Claims 86 and 115 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Harpold in view of Chalfie *et al.*, U.S. Pat. No. 5,491,084 ("Chalfie"). (Office Action, at page 8, lines 6-7.) Applicants respectfully traverse this rejection.

Specifically, the Examiner asserts that Chalfie teaches a method for cells expressing a biological activity (gene expression) of a particular target molecule, wherein the regulatory sequences of a target molecule are linked to a reporter fluorescent protein which fluoresces when the target is expressed within the cells, and that the reporter fluorescent protein is a gene encoding a green fluorescent protein. (Office Action, at page 8, lines 10-14.)

The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of determining the effect of a substance on the biological activities of target molecules as taught by Harpold with the method of detecting the effect of a substance on different target molecules linked to a GFP reporter gene system as taught by Chalfie to achieve an enhanced sensitivity in determining the effect of a substance on biological activity. (Office Action, at page 8, lines 15-19.)

The deficiencies of Harpold have been discussed *supra*. Chalfie merely discloses the use of green fluorescent protein ("GFP") as a reporter gene. Applicants submit that Chalfie does not remedy the deficiencies of Harpold, because there would have been no reason, in light of Harpold and Chalfie, for one of ordinary skill in the art at the time the invention was made to arrive at *simultaneous* application of a test substance from the same supply and under the control of a robot to a set of test cells, as recited in claims 86 and 115, or *simultaneous* application of a test substance from the same supply and under the control of a robot to a set of test cells containing *different* biological target molecules, as recited in claim 86. Thus, Applicants submit that Chalfie fails to overcome the

deficiencies of Harpold, and assert that the Examiner has not met the burden for a *prima facie* case for obviousness.

Accordingly, Applicants believe that the rejection of claims 86 and 115 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Harpold in view of Chalfie has been overcome and respectfully request that the rejection be withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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